

antagonists have a much higher rate of adverse events, especially on cognitive functions, whereas the US guideline felt that if dosed appropriately, these agents could be safely used in the management of CIU.^{2,3,9}

In addition, Weinberger cites a remote publication that demonstrates the efficacy of cyproheptadine for the treatment of cold-induced urticaria.¹⁰ Although this later double-blind placebo-controlled trial was relevant at its time, several trials with single dose and up dosing of nonsedating H1 antagonists with highly superior safety profiles have subsequently been found to be effective for the treatment of cold-induced urticaria.¹¹⁻¹³ It should be noted the international guideline provides a table listing alternative treatments, including first-generation H1 antagonists such as hydroxyzine and cyproheptadine, which can be used for the treatment of CIU depending on the clinician's judgment and the patient's clinical response to second-generation H1 antagonists.² However, these therapies could not be recommended in the final treatment algorithm because of their low scientific evidence based on GRADE analysis and their safety profile.² Weinberger also mentions that the guidelines did not discuss the disease-modifying effect of cyclosporine.^{14,15} However, in the trials cited, this effect was never demonstrated because there was no long-term follow-up of these patients.^{14,15} Furthermore, there are no well-controlled high evidence-based clinical or laboratory studies that address this clinical observation.

We recognize that there are still many significant knowledge gaps in the treatment of CIU and that alternative therapies outside the recommended treatment guideline algorithms may be necessary in difficult-to-manage patients. However, in these situations, both guidelines provide enough leeway for clinicians to structure therapies on the basis of their patient's special needs and individual preferences.

In conclusion, we strongly recommend that clinicians adhere to evidence-based guidelines^{3,9} and endorse the international treatment algorithm because the medications proposed have the greatest scientific merit for controlling most patients with CIU with or without angioedema.

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Intraoperative anaphylaxis: remember the hidden allergens



We read the publication on intraoperative anaphylaxis in a patient with cold urticaria by Maciag et al¹ with great interest. The paper concerns a 15-year-old girl who developed intraoperative anaphylaxis at the time of irrigation of the operative site with cool fluids containing bacitracin, during repair of facial anomalies. The case clearly demonstrates the complexity of allergy investigation after reactions occurring in the perioperative setting. Despite thorough testing for all medications used during surgery and anesthesia using skin testing and challenge testing, for some medications in the outpatient clinic, and the remaining medications during uneventful subsequent surgery, no allergen was identified. The patient had a history of urticaria triggered by exposure to cold temperatures, which could usually be managed with

preventative antihistamine. There is no mention of previous episodes of cold-induced anaphylaxis. As ice cube testing, which is diagnostic for cold urticaria, was positive, and all other testing was negative in a patient with clinical anaphylaxis with a significant increase in tryptase, the authors concluded the cause to be cold-induced anaphylaxis triggered by intraoperative exposure to cool fluids.

Although we agree that this is an important differential diagnosis and congratulate the authors on drawing attention to this rare cause of intraoperative anaphylaxis, we have one concern regarding the investigation of the patient. Although the patient was thoroughly investigated with all intraoperative medications, in the paper, there was no mention of the investigation of possible hidden allergens such as chlorhexidine, latex, ethylene oxide, or excipients. Intraoperative exposure to these substances is almost inevitable and they are all known to cause intraoperative allergy.²⁻⁴ In the Danish Anaesthesia Allergy Centre (DAAC), we test all patients for these potential hidden allergens routinely and we encourage others to do the same. Chlorhexidine deserves special attention because it is widely used in the health care setting, and in DAAC, chlorhexidine is the culprit drug in almost 10% of Danish patients investigated for intraoperative allergy.⁵ The recent NAP6 project on perioperative anaphylaxis in the United Kingdom where all patients were also routinely tested with chlorhexidine found it to be the cause in 9% of cases.⁶ In addition, recently, the American Food and Drug Administration issued a warning about the possibility of rare but serious allergic reactions caused by chlorhexidine.⁷ Consequently, we believe that it is important to remember to test with chlorhexidine and other relevant hidden allergens² in patients with intraoperative allergy.

In conclusion, we appreciate the conclusions drawn in the study by Maciag et al and the focus on an important differential diagnosis in intraoperative anaphylaxis. However, we felt that it was appropriate to draw attention to the hidden allergens in intraoperative allergy and suggest excluding allergy to chlorhexidine, latex, and ethylene oxide and any relevant excipients to make the case for cold-induced anaphylaxis even stronger.

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Reply



To the Editor:

We would like to thank Opstrup and Garvey¹ for their commentary in “Intraoperative anaphylaxis: remember the hidden allergens.” As they suggest, many agents employed during a procedure, from antiseptics to latex, can precipitate an intraoperative reaction in a susceptible individual.¹ These substances are rarely documented in operative notes by the surgeon, or in anesthesia records. We would like to highlight the importance of face-to-face multispecialty collaboration after an intraoperative reaction to prompt consideration of these possible culprits.

In our particular case, the patient did not previously experience cold-induced anaphylaxis outside of the setting of surgery. This may have been related to the lack of a more systemic exposure to cold before her procedure. In addition, many common anesthetic agents cause peripheral vasodilation and thus alter physiologic thermoregulation through a radiative loss of body heat. The physiologic effects of anesthesia likely lowered the threshold for her anaphylactic reaction to the cool fluids. It is likely that this systemic exposure, as well as large surface exposed to cold fluids, precipitated her reaction.

Opstrup and Garvey¹ suggest that latex exposure could have caused anaphylaxis. Uribe et al² report that in pediatric cases, latex is a primary cause of perioperative anaphylaxis, with an incidence of 1 of 10,159 anesthetic events. In pediatric patients with underlying atopy, approximately 4% are sensitized to latex.³ Latex allergy is far more common in those who have had latex exposure intraoperatively in the first year of life.⁴ In hopes of mitigating reactions as well as sensitization in employees as well as patients, all operative suites at Boston Children's Hospital are latex free. It is improbable that latex caused anaphylaxis in this case.

Chlorhexidine is a frequently employed antiseptic and is associated with a high rate of perioperative anaphylaxis.⁵ In pediatric patients as well, chlorhexidine has been reported as a cause of anaphylaxis, but the frequency of this reaction is not known.² To mitigate infectious risk, our patient prepared for days preoperatively with chlorhexidine. Postprocedurally, she continues to use chlorhexidine regularly, and has not suffered a reaction. Consistent use before and after the procedure without reaction makes it improbable that chlorhexidine caused anaphylaxis in her case.

In their operative notes, surgeons diligently describe the technique employed during the procedure, but they rarely mention medications or topical products used. Similarly, the anesthesia record thoroughly recounts antibiotics, paralytics, and sedatives used, but does not reference other potentially allergenic substances used in the case. These “hidden allergens,” as described by Opstrup and Garvey,¹ can indeed cause allergic reaction and even anaphylaxis. We appreciate the importance of this consideration. Furthermore, we would like to highlight the

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